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Dose and outcomes in primary immunodeficiency disorders

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Currently, the principal form of treatment for patients with primary immunodeficiency disorders (PID) in Europe is subcutaneous immunoglobulin (SCIg) replacement therapy. Conversely, until relatively recently, intravenous immunoglobulin (IVIg) replacement was the preferred option for treatment of PID in the United States. Patients with PID are more susceptible to recurrent or severe infections than individuals without PID. A retrospective analysis of data from the European Society of Immunodeficiencies (ESID) registry, between 2004 and 2010, showed marked regional variability in the clinical outcomes of patients with PID receiving SCIg or IVIg replacement therapy [1]. In this analysis, patients receiving IVIg appeared to present with more serious bacterial infections and spend more days in hospital than patients receiving SCIg. Furthermore, in a subgroup of patients, those who switched from IVIg to SCIg replacement therapy spent fewer days in hospital after the switch [1].

However, there are a number of considerations when deciding on the route of immunoglobulin G (IgG) administration. The volume of immunoglobulin (Ig)G that can be given into the subcutaneous (s.c.) space can be limited when compared with the volume that can be delivered intravenously (i.v.); thus, SCIg must be administered more frequently than IVIg. SCIg treatment regimens include weekly, bi-weekly or daily push doses that can be self-administered. Typical regimens for the i.v. route of administration are once every 3–4 weeks given at home or in a clinic setting. In contrast to the cycle of peak and trough serum IgG levels following IVIg infusion, SCIg regimens produce minimal variation in trough serum IgG levels [2]. Systemic side effects are more common with IVIg than SCIg, and infusion site reactions are more common with SCIg, particularly during the early phase of s.c. IgG replacement therapy [2,3]. An alternative method to facilitate SCIg administration is a pre-infusion of recombinant hyaluronidase followed by a monthly dose of s.c. IgG. This method has been reported to have a low rate of systemic side effects, similar to conventional SCIg [4].

The impact of home-based monthly IVIg and weekly SCIg self-infusions on health-related quality of life (HRQoL), treatment satisfaction and patient preference for either IgG replacement venue has been investigated in patients with PID treated previously with IVIg in the hospital or at home [5]. Patients who switched from hospital-based IVIg to IVIg or SCIg self-infusions at home reported significantly fewer limitations with work/daily activities, significantly improved quality of life (e.g. feeling of more energy, less tiredness and fatigue) and better general health. While s.c. IgG were preferred over i.v. infusions by PID patients, overall patient satisfaction and preference for IgG replacement therapy was linked to home IgG therapy [5]. Specifically, the effect on improving the quality of life (QoL) for PID patients was less striking in the switch from home-based IVIg to SCIg self-infusions at home; home therapy was the major factor in improving QoL [5].

Administration of IgG via the s.c. route is becoming increasingly popular in the United States, and in a survey of European and US clinical immunologists the majority of respondents agreed that IgG administered s.c. is as effective as IVIg therapy [6]. However, the question still remains as to the optimal dosage regimen that provides the best clinical outcome in preventing serious and/or recurrent infections in patients with PID. Progressive increments in the dose of IVIg produce linear increases in trough IgG levels, leading to a 27% decline in the incidence of pneumonia with every 100 mg/dl increase in trough IgG up to at least 1000 mg/dl [7]. Similarly, higher SCIg doses have been shown to also correlate with higher serum IgG levels. However, although higher IgG serum levels achieved by SCIg infusions correlated with lower rates of non-serious infections, there was no correlation between the SCIg dose administered and the rate of infection in this study [8]. Nevertheless, higher SCIg doses appeared to provide improvements in a

number of clinical outcomes, including fewer days in hospital, fewer days on antibiotics and a reduced annual rate of infection [8].

Although targeting a serum/trough IgG level that raises IgG levels above 500 mg/dl is a useful guide in beginning IgG replacement therapy for patients with PID [7,8], in healthy individuals there is a wide variation in serum IgG levels well above this 'targeted' serum IgG level [9]. Furthermore, the level of serum IgG that protects patients with PID against recurrent or serious infections is likely to vary widely for each patient, as it does in healthy individuals [9]. The suggested goal of therapy should be to identify the individual 'biological' serum IgG trough level required to maintain a PID patient as infection-free as possible [10]. The 'biological' level can be obtained by charting a patient's serious or recurrent infections against their IgG levels over time, and is a 'moving target' because it can be altered by changes in clinical status, such as changes in body weight, pregnancy or the development of co-morbid conditions, such as renal [10] and gastrointestinal disease. The concept of targeting an individual PID patient's 'biological' IgG level is supported by data obtained by a large cohort of patients with common variable immunodeficiency (CVID) or X-linked agammaglobulinaemia (XLA) who were followed-up over a period of 22 years [11]. This study clearly showed that there is a wide range of serum IgG levels that were required to keep these PID patients as infection-free as possible, and that only some PID patients need the largest doses of IgG that have been shown to reduce the development of pneumonias [7]. In addition, there was variability in the amount of IgG required to keep CVID *versus* XLA patients healthy, suggesting that the original IgG repertoire present in CVID *versus* XLA patients may be important in determining the IgG dose required to keep these two different PID patient populations healthy. Moreover, the wide variation in the dose of IgG used to keep PID patients healthy did not exceed the wide range of serum levels found in healthy, age-appropriate individuals.

A 5-year prospective study identified subgroups of patients with PID at high risk of infection [12]. CVID patients had a high risk of pneumonia if they had low IgG and IgA levels at diagnosis or an IgA level <7 mg/dl with bronchiectasis. In XLA, the only co-morbidity risk factor identified for pneumonia was the presence of bronchiectasis [12]. Although this remains controversial, PID patients with bronchiectasis appear to require higher doses of IgG to achieve the same trough IgG level as those without this disease [11]. Use of higher doses of IVIg that provides IgG levels >500 mg/dl may be required to decrease the incidence and progression of bronchiectasis in patients with XLA and CVID [13]. In another 2-year prospective study, IgG trough levels >600 mg/dl were shown to be better in controlling bacterial infections and pulmonary complications in patients with CVID [14]. In addition, doses of 800–>1100 mg/dl have been shown to produce a slower decline in age-associated pulmonary function tests in adults with PID [15].

In conclusion, individualizing the IgG dose and route of administration, together with identification of a given PID patient's 'biological IgG level', helps prevent severe and recurrent infections. In addition, individualization of therapy can improve adherence and improve the QoL of PID patients by allowing each individual patient to choose the IgG replacement venue that best suits their lifestyle. Finally, the goal of IgG replacement therapy is to provide sufficient amounts of IgG, by the i.v. or s.c. route, to minimize serious and recurrent infection. This can be achieved by identifying and then maintaining each PID patient's 'biological IgG level' that can vary over time depending on the development of co-morbid conditions.

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